Conducting and reporting trials for older people

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Abstract

Randomised controlled trials provide the most rigorous test of efficacy and effectiveness for interventions used in healthcare. They underpin much of clinical practice, yet older people are often excluded from studies, resulting in uncertainty about risks and benefits of new treatments.

Encouraging inclusion of older people in randomised controlled trials and reporting of trial results in a rigorous manner is a key function of clinical geriatrics journals such as Age and Ageing. This article provides practical advice on how to report randomised controlled trials that are targeted at older people. Some of these issues are generic, but there are specific requirements which apply to most studies of older people. Recording and reporting basic characteristics of recruits in terms of physical function, cognition, co-morbidity and / or frailty is vital to allow proper interpretation of the external validity of the trial. Adverse effects should include consideration of common geriatric problems including falls.

Authors should follow the CONSORT reporting guidelines (CONsolidated Standards Of Reporting Trials) to enhance the transparency and quality of their manuscript.

Key words

Research methods, randomised controlled trials, older people

Key points

- Encouraging inclusion of older people in randomised controlled trials and reporting of trial results is a key function of clinical geriatrics journals such as Age and Ageing.
- This article gives advice on manuscript preparation, which if followed, should enhance the clinical impact of the research, and minimise the risk of research waste.
- Age and Ageing follows the recommendations of the International Committee of Medical Journal Editors (ICMJE), which requires registration of clinical trials in a public trials registry.
- It is recommended that authors follow the CONSORT reporting guidelines in their manuscript preparation.

Background

Randomised controlled trials provide the most rigorous test of efficacy and effectiveness for the interventions used in healthcare. They underpin much of clinical practice and many guidelines, yet older people (and particularly those who are frail or carry high levels of co-morbidity) are often excluded from studies [1], resulting in uncertainty about risks and benefits of new treatments for older people [2].

Encouraging inclusion of older people in randomised controlled trials and reporting of trial results is therefore a key function of clinical geriatrics journals such as *Age and Ageing*. This article gives advice, which if followed, should enhance the clinical impact of the research, and minimise the risk of research waste [3]. Some of these issues are generic, but there are also specific reporting requirements which apply to most trials for older people. This article provides practical advice on how to report randomised controlled trials that are targeted at this sector of the population. However manuscript preparation and reporting does not however occur as an isolated activity; the advice that is provided is relevant to the whole process of trial conduct, from conception to design, running of the study and analysis.

General points

Writing a high-quality clinical trial report is much easier if the study has been well designed; this includes recruitment of an appropriate number of participants, low dropout rate, use of clinically relevant outcomes and a well-structured, pre-determined analysis plan. The best writing cannot rescue a poorly-designed trial. Thus the process of producing a high-quality report starts at the point of conceiving the need for the trial. It is also useful perhaps to consider some of the issues that lead to rejection of manuscripts:

- Is the study question important to patients, carers and to clinicians? *Age and Ageing* is a clinical journal, and so we expect the trial outcome to be clinically relevant.
- Was the trial registered prospectively on a recognised trials database? e.g. https://clinicaltrials.gov.

Box 1.

Age and Ageing follows the recommendations of the International Committee of Medical Journal Editors (ICMJE), which requires registration of clinical trials in a public trials registry at or before the time of first patient enrolment as a condition of consideration for publication (see http://www.icmje.org/recommendations).

- Is there a clearly stated primary outcome?
- Is the study adequately powered for the primary outcome?
- If it is possible to blind (mask) participants and researchers to the trial intervention, has this been done, and are the methods adequate?
- Was the randomisation process adequate, and was allocation concealment preserved?
- Is sufficient information provided on the patient cohort to allow the reader to judge external validity and relevance of the findings?
- Is the study population appropriate to the research question?
- Are the outcomes analysed as set out at the start of the trial in a pre-defined statistical analysis plan?

Practice in the conduct and reporting of trials has been substantially improved by methodological initiatives such as CONSORT (CONsolidated Standards Of Reporting Trials) [4] and its various extensions (available through the EQUATOR network: Enhancing the Quality and Transparency Of health Research; http://www.equator-network.org/). Completion of the CONSORT checklist and submission

as a supplementary file is encouraged, as this demonstrates explicitly that the trial report follows the guidelines.

> Box 2.
>
> Age and Ageing recommends that authors follow the CONSORT reporting guidelines [4] (available through the EQUATOR network: Enhancing the Quality and Transparency Of health Research; http://www.equator-network.org/).
>
> Completion of the CONSORT checklist and submission as a supplementary file is encouraged.

Whilst any trial design involves compromises, and there is no such thing as a perfect study, the issues highlighted above are inherent to the design of a good trial. As such, they cannot be remedied at the stage of writing the trial report. Some other issues are important and are covered in the sections below, but will not necessarily lead to rejection on their own – often because they can be remedied at the writing stage. These include results presented in a way that is difficult to understand, discussion not covering areas recommended by the CONSORT statement, or conclusions not being supported by the data.

Specific sections of the paper:

The abstract

Providing a clear well written abstract to accompany the paper (or for conference proceedings) is vital. The CONSORT extension on abstracts is highly recommended [5] ; it gives a list of essential items that should be considered. Authors should be mindful that often the abstract is the only part of the full paper that is read, and so it is essential that this summary of the work is both clear and accurate.

The Introduction

Every paper tells a story, and the introduction is where the story starts. The author should use the introduction to make three things clear. Firstly, why is the issue important? Secondly, what evidence already exists – eg are there published pilot data or a systematic review that provides initial evidence of possible efficacy? Thirdly, what is the gap that this trial aims to fill – or in other words what is the uncertainty that the trial aims to address? Readers of *Age and Ageing* are generally aware that the number of older people in the world is increasing and that there is a need to find better methods of care; therefore it is not necessary to state these very general points.

The Methods

With the advent of on-line supplementary information in journals, including *Age and Ageing*, there is no excuse for incomplete methods. The information critical to telling the story of the paper should be included in the main text, but additional detail can be put into supplementary information. Some key issues that are important in the methods section are listed below, using the PICO format:

Population: Tell the reader who you recruited (inclusion and exclusion criteria), where you recruited the participants from, and how you recruited them. Justify why you used exclusion criteria; was it because of safety, targeting a group most likely to benefit, or because of inability to perform certain outcomes?

Intervention: Sufficient detail is required so that the intervention can be replicated. This is straightforward for most pharmacological interventions, but requires more information for complex interventions such as exercise programmes. Consider describing the intervention in detail in supplementary (on-line only) material, and also consider providing links to any relevant manuals, which should be publicly available.

Comparator: If usual care is the comparator, describe what this comprises. *Age and Ageing* is an international journal, and many readers may be unfamiliar with how health services work in the country that hosted your trial. Understanding the setting and processes of usual care is essential to judge generalisability.

Outcomes: The method for collecting or measuring each outcome should be described in sufficient detail for others to be able to replicate. Justification for the choice of outcomes is needed; this justification should include reference to the original methods paper and evidence of validation of the method, ideally in a relevant population of older people. State what the primary outcome is; this should have been decided before the start of the trial. Note that there usually should be only one primary outcome; if two outcomes are nominated as co-primary outcomes, this should be stated explicitly and should be reflected in how the sample size calculation is constructed (usually by splitting the alpha in the sample size calculation). Offering multiple primary outcomes is strongly discouraged.

Randomisation and blinding: The method used for randomisation should be described in detail; it is not sufficient to merely state that randomisation took place. What method was used – computer generated lists, pre-prepared envelopes, web or telephone based interactive randomisation systems? Sequence generation, allocation concealment and mechanism of implementation should all be covered. The key issue here is to give sufficient detail to reassure readers that the process was robust and unlikely to be subject to manipulation. Using web or telephone based systems run by a third party not otherwise involved in the conduct of the trial is preferable to other methods for this reason.

Similarly, for blinding (or 'masking'), authors should be explicit about who is blinded. Participants? Researchers measuring outcomes? Supporting clinical staff? Blinding of researchers can almost always be employed for outcome measures even if other aspects are harder to blind. When blinding is used, how successful was the blinding? Giving some data to support this (e.g. a description of whether the

research team measuring outcomes could guess group allocation) gives reassurance to readers that the blinding process did work.

Analysis: Include a sample size calculation, which should have been done before the start of the trial. Sample size calculations are often inadequately reported, often with basic errors or omissions, and frequently based on assumptions that are inaccurate [6]. Usually four elements of information should be provided; type I error (conventionally 5% is the maximum accepted), power (usually a minimum of 80% is expected), assumptions in the control group (response magnitude and standard deviation), and expected treatment effect. The sample size should be based on the primary outcome, should mirror how the primary outcome is to be analysed, and should contain sufficient detail for a statistician to replicate the calculation. Consider carefully whether the likely size of effect of the intervention is plausible and clinically relevant. Can the effect be 'benchmarked' against an intervention of known proven benefit (eg effect of Comprehensive Geriatric Assessment on mortality)? Is there data available on the minimum clinically important difference that can inform the effect size that is sought?

Be explicit about how the outcomes were analysed; what tests were used, what statistics package was used, what statistical assumptions were tested prior to the analysis, and how missing data were handled. For most trials involving frail older people, missing data are inevitable. Last value carried forward approaches, or exclusion of those with missing data, often are not helpful and carry substantial risk of bias. Use of multiple imputation or mixed model approaches provide alternatives to minimise such biases.

Related to this, state whether the analysis was done by intention to treat, modified intention to treat, or per-protocol, but state clearly what population was analysed, as these terms may cover a multitude of analytic choices. In general intention to treat approaches are to be preferred as the primary analysis, to reduce the risks of selection bias that come with adherence. Per-protocol analyses can however provide useful secondary data to help understanding of the potential magnitude of effect of 'sticking with' an intervention.

Box 3.

Intention to treat approaches to data analysis are recommended as the primary statistical methodology.

Per-protocol analyses can provide useful secondary data to help understand the potential magnitude of effect of an intervention. However this approach carries high risk of bias due to differential selection of subjects who adhere to treatment (or control group) allocation.

The Results

Describing the trial population

When choosing what to include in the baseline descriptors table (which is usually Table 1 of any trial), authors should picture themselves as practising geriatricians reading the trial paper. What would they want to know? The baseline descriptors table needs to give sufficient information that the reader can judge whether the trial population was similar to that seen in clinical practice. This means not only giving age, sex, and details pertinent to the condition under study, but a range of information pertinent to the care and characterisation of older people. Suggested details to include in any clinical trial for older people are given in Table 1. As well as helping the reader understand the characteristics of the population under study, the baseline table is vital in showing whether the intervention and control groups were well matched for possible confounders. The statistical methods of summarising relevant descriptive data are well described by Pickering in a recent review article in this journal [6] .

Participant flow through the trial

A CONSORT flow diagram is a central part of reporting any trial, and is crucial to understanding the generalisability of the results [4] . Both numbers and reasons for dropouts at each stage of the trial should be provided, and numbers available for analysis given for each time-point. An often neglected part of the CONSORT diagram is information on how many potentially eligible participants were

approached; this information not only helps the reader to decide how generalizable the results are (if only 2% of potentially eligible participants take part, generalisability is less than if 50% take part), but also helps future trialists plan how many people they will need to screen in order to recruit their target number.

The Primary outcome

Table 2 should usually contain the primary outcome analyses. The primary outcome is the most important part of the results – it is the main reason for having conducted the trial. It therefore follows that the space devoted to the primary outcome should be a significant part of the results. The primary outcome, and any pre-planned subgroup analyses, should be presented in this table. Sensitivity analyses often will be better placed in a supplementary on-line only appendix. The most helpful way to present outcome data varies , but in general, it is most informative to give summary values for each group at each time-point, and also between-group differences with 95% confidence intervals (i.e. treatment effect), which may be derived from a repeated measures analysis or given for a single, pre-specified time-point. Giving information in both of these ways makes the size of the treatment effect clear to readers and facilitates the work of those undertaking systematic reviews and meta-analysis [7].

Secondary outcomes

These are by definition much less important than the primary outcome. In many trials, there is insufficient power to detect clinically relevant effects on secondary outcomes. Furthermore, if the study includes multiple secondary outcomes, statistically significant results will often be obtained by chance (type 1 statistical error). It therefore follows that fewer is often better when it comes to secondary outcomes – both in trial design and trial reporting.

The author should consider what secondary outcomes are essential, and focus on reporting these in the main paper. Report the other secondary outcomes, but consider placing these in supplementary

data. Avoid selective reporting of only the 'most interesting' or positive secondary outcome results. This leads to bias, potentially overstating the benefits from an intervention. In a similar, but related vein, be very cautious about *post-hoc* subgroup analyses. Such analyses are notoriously unreliable (for similar reasons of power and multiple testing described above), carry little credibility, and distract from what should be the main focus of a trial report. Such analyses are sometimes performed to find positive results in a trial which was negative; this is not appropriate. *Age and Ageing* welcomes trials with null results as long as they are well designed and the negative result is credible.

Adverse events

Adverse events are often poorly reported [8]; such information is essential to appraise the potential harms of an intervention. Just as outcomes in trials involving older people need to capture potential benefits across a range of functional and organ domains, harms may occur in unexpected ways. Hence the reporting of adverse events needs to include harms across all organ systems and functional domains – not just those thought to be relevant to the intervention or condition under scrutiny. An example would be a trial of blood pressure medication – adverse effects on renal function would commonly be reported as a harm, but few trials of antihypertensives report falls as an adverse outcome [9], despite this clearly being highly relevant both to older people and to geriatricians. A further benefit of thorough reporting of adverse events is that they help the reader to judge whether the trial population resembles that seen in clinical practice. Older, frail people are often sick and have a high number of illness events in the real world. Trial populations with few adverse events are therefore likely to be rather fitter than the population seen in clinical practice, again questioning the generalisability of the results. A table of adverse events, including care home placement, hospitalisation and death, should usually be included in the supplementary information, with some comment on event rates in the main paper.

Presenting results and statistics

A good principle to follow is that statistics are there to confirm what is obvious by inspecting the data. Giving statistical test results as p-values without clear simple summaries of effect of the intervention on the outcome measures is not adequate is this does not allow the reader to understand what the results mean in terms of clinical impact.

Box 4.

Reporting effect size and statistical significance:

For each primary and secondary outcome, provide results for each group, the estimated effect size (between group difference) and its precision (usually a 95% confidence interval). This should be accompanied by statistical significance (p-value), however reporting this on its own is not sufficient to enable interpretation of the clinical relevance of the results.

Statistical methods should be described with enough detail that a knowledgeable reader with access to the original data could verify the reported results (www.icmje.org). They should follow an *a-priori* statistical analysis plan [10] .

The discussion and conclusions

It is good practice to structure the discussion section according to the advice in the CONSORT statement [4]. This not only ensures coverage of all key aspects of the discussion, but also restricts the latitude for unsupported opinion and speculation. A summary of limitations is a key component. The discussion also needs to compare the findings with what others have reported, suggest reasons for any divergent results, and should also place the findings into their clinical context – in particular, it

should comment on the generalisability and applicability (external validity). Consider how the results might impact on clinical practice, health policy and future research. If one conclusion is that more research is required, be specific about what is needed – a bigger trial, a trial of a different intervention, or a trial in a different population?

Avoid exaggerations and excessive speculation – there is the risk of both misleading the reader and loss of credibility of the report. Conclusions should be worded conservatively, and supported by the data given in the results.

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None

Conflicts of interest

DS and MDW are editor-in-chief and deputy editor of *Age and Ageing*

References

1. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials 2015;16:495.
2. Watts G. Why the exclusion of older people from clinical research must stop. BMJ : British Medical Journal 2012;344.
3. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet 2009;374:86-9.
4. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Bmj 2010;340:c869.
5. Hopewell S, Clarke M, Moher D, et al. CONSORT for reporting randomised trials in journal and conference abstracts. The Lancet 2008;371:281-3.
6. Pickering RM. Describing the participants in a study. Age and Ageing 2017;46:576-81.
7. Shenkin SD, Harrison JK, Wilkinson T, Dodds RM, Ioannidis JPA. Systematic reviews: guidance relevant for studies of older people. Age Ageing 2017:1-7.
8. Maggi CB, Griebeler IH, Dal Pizzol Tda S. Information on adverse events in randomised clinical trials assessing drug interventions published in four medical journals with high impact factors. The International journal of risk & safety in medicine 2014;26:9-22.
9. Mulrow C, Lau J, Cornell J, Brand M. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev 2000:Cd000028.
10. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj 2013;346:e7586.
11. Freiberger E, de Vreede P, Schoene D, et al. Performance-based physical function in older community-dwelling persons: a systematic review of instruments. Age and Ageing 2012;41:712-21.
12. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing 2011;40:423-9.
13. Fritz S, Lusardi M. White Paper: "Walking Speed: the Sixth Vital Sign". Journal of Geriatric Physical Therapy 2009;32:2-5.
14. Hodkinson HM. Evaluation of a mental test score for the assessment of mental impairment in the elderly. Age Ageing 1972;1:233-8.
15. Damian AM, Jacobson SA, Hentz JG, et al. The Montreal Cognitive Assessment and the mini-mental state examination as screening instruments for cognitive impairment: item analyses and threshold scores. Dementia & Geriatric Cognitive Disorders 2011;31:126-31.
16. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Maryland State Medical Journal 1965;14:61-5.
17. Fillenbaum GG, Smyer MA. The development, validity and reliability of the OARS multidimentional functional assessment questionnaire. Journal of Gerontology 1981;36:428-34.
18. Yurkovich M, Avina-Zubieta JA, Thomas J, Gorenchtein M, Lacaille D. A systematic review identifies valid comorbidity indices derived from administrative health data. Journal of Clinical Epidemiology;68:3-14.
19. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2001;56:M146-M56.
20. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ : Canadian Medical Association Journal 2005;173:489-95.
21. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and Ageing 2016;45:353-60.

Table 1: Key baseline characteristics for describing older populations included in clinical trials

Attribute	*Notes / examples*
Age	Mean (or median) age in years and range of dispersion (SD, range). If predetermined subgroups eg ≥80 years of age then give numbers in subgroups.
Sex	Numbers of men and women
Physical function	Short Physical Performance Battery [11]; grip strength [12]; walking speed [13]. Numbers using walking aids (sticks, walking frames)
Cognition	Abbreviated Mental Test score [14]; Montreal Cognitive Assessment (MoCA); Mini-mental state examination [15].
Basic and instrumental activities of daily living	Barthel score [16]; Functional Independence Measure; Instrumental Activities of Daily Living Scale [17] .
Comorbid disease and its treatment	Include all disease areas, not just those relevant to the direct focus of the trial intervention. Charlson comorbidity index, medication count [18]; categories of medications.
Frailty	Fried frailty phenotype [19]; Rockwood frailty index [20]; electronic Frailty Index [21] . May provide a useful summary of several of the above components
Living arrangements	Numbers living alone. Numbers in standard housing, supported living, sheltered housing, care home.

	Formal help received (home help, district nurses).